Complete Summary

GUIDELINE TITLE

Guidelines for the performance of the sweat test for the investigation of cystic fibrosis in the UK.

BIBLIOGRAPHIC SOURCE(S)

Guidelines for the performance of the sweat test for the investigation of cystic fibrosis in the UK. London: Royal College of Paediatrics and Child Health; 2003 Nov 1. 97 p. [123 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Cystic fibrosis (CF)

GUIDELINE CATEGORY

Diagnosis

CLINICAL SPECIALTY

Internal Medicine
Pediatrics
Pulmonary Medicine

INTENDED USERS

Advanced Practice Nurses
Clinical Laboratory Personnel
Physician Assistants
Physicians
Respiratory Care Practitioners

GUIDELINE OBJECTIVE(S)

To produce guidelines on how to perform the sweat test for the investigation of cystic fibrosis in the United Kingdom with emphasis on:

- Organisation/delivery for patient care (including patient/parent information)
- Sweat collection (including subject suitability)
- Sweat analysis
- Quality of the testing
- Interpretation of results (including false positives; indications for repeat analysis; use of other tests)
- Who should do the collection and analysis
- Assessment of competence and training needs

TARGET POPULATION

Children aged 0-18 years with one or more of the following indications:

- Phenotype suggestive of cystic fibrosis (CF)
- Family history of cystic fibrosis
- A positive newborn screening test
- Suspicion of an atypical phenotype

INTERVENTIONS AND PRACTICES CONSIDERED

Sweat test for cystic fibrosis, including the following aspects of testing:

1. Providing patient and parents with information and obtaining informed consent
2. Ascertaining subject suitability
    - Clinical state
    - Exclusions/restrictions
3. Sweat collection
    - Site of collection, avoidance of contamination, and number of collections
    - Stimulation methods and equipment (power supply and electrodes, electrolyte solutions [e.g., pilocarpine, magnesium sulphate solutions], iontophoresis time and current, safety precautions)
    - Collection medium/time/containers
4. Sweat analysis
    - Weighing
    - Elution of sweat from filter paper
    - Analytes (chloride and sodium recommended); sweat conductivity (osmolality considered but not recommended)

- Analytical methods (calorimetry, coulometry, indirect ion selective electrode, direct ion selective electrode, flame photometry)
- Reporting format

5. Quality control
   - Internal quality control
   - External quality assessment
   - Audit
6. Reference values and interpretation
   - Definitions
   - False positives
   - Repeat testing
   - Use of other tests
7. Responsibility for testing and training
   - Responsibility for sweat testing
   - Who should perform sweat testing?
   - Competence/training issues

MAJOR OUTCOMES CONSIDERED

- Accuracy and precision of testing procedures for diagnosis of cystic fibrosis
- Incidence of false-positive and false-negative test results
- Safety of testing procedures

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The search process comprised the following:

- Searching of computerised databases
  - Medline 1965-2001
  - Human studies
  - Children 0-18 years
  - All types
  - Reviews, meta-analyses, searched on sweat tests, editorials, clinical trials, letters, etc.
- Hand searching
  - Text books and review articles
  - Review of existing literature assembled by expert group members
  - Selected articles pre 1965
  - Personal contact with recognised national and international experts - UK, USA, Australia
- Specific searching:

For particular sections of the report, specific searching as detailed below was undertaken:

Sweat collection

1. Published articles on sweat test combined with:
    - Iontophoresis
    - Burns
    - Urticaria
    - Apparatus
    - Equipment

2. Review of questionnaire data collected for sweat test workshops from 30 centres (Association of Clinical Biochemists National Meeting 1998 and UK National External Quality Assessment Schemes Workshop 1998)
3. Wescor instruction manuals (Webster sweat collection system model 3500. 1979; Macroduct sweat collection system model 3600-sys 1983) and Website (http;//www.wescor.com)
4. Data collected by Internet enquiry (Association of Clinical Biochemists Mailbase) and personal contact with colleagues in UK, USA, and Australia.
5. Information supplied by Wescor, Inc., via Chemlab Scientific Products, Astra House, Christy Close, Southfield Business Park, Laindon, Essex, SS15 6TQ, in response to enquiry.

Sweat Analysis

1. Searched on Medical Subject Headings (MeSH) vocabulary for Sweat Test. No exact match, except for the following:
    - Sweat
    - Sweating
    - Gland, Sweat
    - Testing
    - Searched on: Iontophoresis, burns, urticaria, equipment, and supplies
    - Used a combination of MeSH and keyword or textword searching

2. UK National External Quality Assurance Schemes Sweat Test External Quality Assurance Surveys

Quality

1. UK Audits on Sweat Testing (unpublished data)
2. UK National External Quality Assessment Schemes Data from Sweat External Quality Assessment Surveys
    - Review of existing Consensus Based Guidelines
        - National Committee for Clinical Laboratory Standards (NCCLS) 2000
        - Welsh Sweat Standard 1999

- National UK Laboratory Sweat Test Subgroup
    - This comprises evidence from a 'Consensus of experts' collected from the National UK Laboratory Subgroup
    - Under the chairmanship of Dr. J. Kirk, the subgroup was made up of: Birmingham Children's Hospital (Dr. A. Green), Edinburgh Royal Hospital for Sick Children (Dr. J. Kirk), Great Ormond Street (Dr. Tony Reynolds), Sheffield Children's Hospital (Dr. J. Bonham), Southend Hospital (Mr. M. Fahie Wilson), UKNEQAS (Mr. Finlay McKenzie). The group discussed data that had been collected by a precirculated questionnaire. Data was collected from the meeting participants and also from Belfast Sick Children's Hospital (Ms. G. Roberts), Bristol Children's Hospital (Dr. J. Stone), University Hospital, Cardiff (Ms H. Losty), Glasgow Royal Hospital for Sick Children (Mrs. M. Rae), St James University Hospital, Leeds (Dr. L Shapiro), Liverpool Children's Hospital (Dr. D. Isherwood) and Manchester Children's Hospital (Dr. M. Addison). Data was collected on site of collection, number of collections, equipment, collection time, minimum sweat rate, definition of upper limit of reference range and lower limit of CF range and methodology.
    - The evidence base for the guidelines was updated during the course of the guideline development process to take account of newly published evidence and evidence arising from the open review meeting/consultation process.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

The levels of evidence are based on the U.S. Agency for Health Care Policy (AHCPR) 1992

I a: Evidence obtained from meta-analysis of randomised controlled trials

I b: Evidence obtained from at least one randomised controlled trial

II a: Evidence obtained from at least one well designed controlled study without randomisation

II b: Evidence from at least one other type of quasi-experimental descriptive study

III: Evidence obtained from well designed, nonexperimental descriptive studies such as comparative studies, correlation studies and case studies

IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Note: The guideline development group felt that the Scottish Intercollegiate Guidelines Network (SIGN) criteria, particularly IIb and III, are sometimes difficult to interpret in the context of performance of a laboratory diagnostic test. The working group has interpreted these levels as follows:

IIb

- A planned scientific study with hypothesis
- A study not controlled
- An experimental study, with a low risk of bias

III

- Nonexperimental/observational study
- Investigation of a standard procedure

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The Working Group has undertaken a systematic review of evidence in accordance with Scottish Intercollegiate Guidelines Network (SIGN) methodology and the evidence and recommendations have been graded according to this. The working group note that the SIGN grading system had been revised since work on these guidelines commenced. It was felt that the revised version offered no advantage in this instance and, therefore, after consultation with the Royal College of Paediatrics & Child Health, the original SIGN version has been used.

Additional points of note are:

- Publication was not considered essential to be considered as good evidence.
- Where several pieces of evidence relate to the same topic, an 'overall evidence' level has been assessed.
- Because it is unethical to undertake controlled trials (randomised or otherwise) to evaluate variability in the performance of the sweat test, there are little data which qualify as grade I or grade II evidence.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Working Group was formed in October 2000 and met on 6 occasions throughout 2000/1/2. The process for guideline development undertaken by the Working Group is summarised as Figure 1 of the original guideline document.

Formulation of recommendations was reached by consensus agreement of the working group members.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading of Recommendations

The criteria for the grading of recommendations in this document are based upon those used by the U.S. Agency for Health Care Policy and Research (AHCPR), and published by the Scottish Intercollegiate Guidelines Network (SIGN)**

A (levels I a and I b): Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation

B (levels II a, II b, III): Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of the recommendation

C (level IV): Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality

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COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This guideline was issued from the Working Group in draft form in July 2002, and in final form in November 2003 after incorporation of comments from the formal appraisal by the Royal College of Paediatrics and Child Health.

Consultation and Peer Review

1. Discussion forum

   The first draft of the guideline was presented to the Cystic Fibrosis Trust Directors (September 7th September 2001) and at an open meeting for all professionals/patient group representatives on November 13th 2001 (see Appendix 3 of the original guideline document).

   Comments and new evidence resulting from these meetings were subsequently considered by the working group at a meeting on November 14th, 2001.

2. Web

   Draft guidelines were made available on the following Web sites during November and December 2001 and January 2002:

   Association of Clinical Biochemists

   The Royal College of Pathologists informed members of the availability of the guidelines with an invitation for comment

   United Kingdom National External Quality Assessment Schemes (UKNEQAS)

3. Consultation

   Views of interested parties not on the working group have been addressed by circulation of the draft guidelines to:

   Wescor Inc., LOGAN, Utah, U.S.A.

   Clinical Pathology Accreditation (UK) Ltd., 45 Rutland Park, Botanical Gardens, SHEFFIELD, S10 2PB

   UKNEQAS,P.O. Box 3909, BIRMINGHAM, B15 2UE

   Comments arising from this consultation period were addressed by the working group chairman in consultation with group members. A consensus agreement was reached by the group for each comment.

4. Specialist Independent Peer Reviewers

The guidelines were reviewed by a panel of independent expert peer reviewers. Comments were addressed by the working group at a meeting on February 19th, 2002 and consensus agreement reached. The draft guidelines were modified in response to the reviewers' suggestions.

Please refer to the original guideline document for a list of the names and addresses of the independent peer reviewers.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Levels of evidence and recommendation grades are defined at the end of the "Major Recommendations" field. An asterisk is used to note changes in recommendation grades following the appraisal process.

Patient Information	Grade	References
• It is good clinical practice to prepare the patient and, where appropriate, parent effectively before testing. Informed consent should be obtained in accordance with local policy. Pretest information appropriate for the individual should include why the test is being done, how it will be performed, risks associated with the test, what the subject will experience, and contact details regarding the testing and final result. An example leaflet for patients/parents is provided (see Appendix document 1 of the original guideline document).	C	
Subject Suitability		
• Sweat tests can be performed after 2 weeks of age in infants greater than 3 kg who are normally hydrated and without significant systemic illness	C	
• Sweat testing can be attempted in term infants after 7 days of age if clinically important, but	C	

Patient Information	Grade	References
will need repeating if insufficient quantity of sweat is collected.		
• Sweat tests should be delayed in subjects who are dehydrated, systemically unwell or who have eczema affecting the potential stimulation sites.	C	
• Sweat tests should be delayed in subjects who are oedematous and/or on systemic corticosteroids.	C	
• Sweat tests should not be performed in subjects who are on oxygen by an open delivery system. This would not apply to an infant in headbox or on nasal prong oxygen.	C	
• Sweat tests can be performed in subjects on flucloxacillin.	C	(Williams et al., 1988)
Sweat Collection		
• The flexor surface of either forearm is the preferred site for sweat collection. Consideration may be given to other sites if both arms are eczematous, too small or otherwise unsuitable. Other sites used successfully include the upper arm, thigh and back.	C	
• Great care must be taken at all stages of the procedure to avoid contamination (see example standard operating procedure [SOP] in the original guideline document).	C	
• In response to a sweat test request it is sufficient to carry out one sweat collection only.	Not Graded*	(Reynolds, personal communication)
• The power supply used must be battery powered and should	C	

Patient Information	Grade	References
include a safety cutout. • Monitoring of the current must be carried out throughout iontophoresis where possible. Wescor systems from model 3600 onwards have no ammeter but have an appropriate safety cut out system. • The power supply and electrodes must be regularly checked, maintained and records kept. • Electrical safety of all power supplies must be checked annually.		
• Electrodes should be of a suitable size and curvature to fit snugly on the patient's limb. • They are most commonly made of copper or stainless steel. • Electrodes should be firmly secured in position to the electrolyte support pads or gels using straps that are adjustable to fit the patient (e.g. Velcro or rubber). • Electrodes must be regularly cleaned and inspected, and discarded if they show pitting or irregularities.	C	
• Selection of new equipment, and maintenance of existing equipment, must comply with Clinical Pathology Accreditation (CPA) (or equivalent standard).	C	
Electrolyte Solutions • Aqueous solutions or Wescor gel discs containing pilocarpine	B	(Price & Spencer, 1977; Szabo, Kenny, & Lee, 1973)

Patient Information	Grade	References
nitrate at 2-5 g/l are recommended for use at both electrodes. Alternative solutions (e.g. magnesium sulphate) may be used at the cathode.		
• Solutions containing sodium and/or chloride should be avoided because of the risk of contamination of the collection.	C	
• Unbuffered acid solutions should not be used because of the increased risk of burns.	B	(Schwarz, Sutcliffe, & Style, 1968)
• Electrolytes used for iontophoresis must either be obtained as part of a medical device (e.g. Wescor Pilogel Discs) or from a recognised manufacturer of unlicensed medical products. Solutions must not be produced in-house by hospital laboratories.	C	
Electrolyte Supports • Suitably thick pads must be used for the electrolyte solutions to minimise the risk of acid burns.	B	(Schwarz, Sutcliffe, & Style, 1968)
• Pads of Hospital Lint BPC Plain 500 gram folded to provide 4-8 thicknesses (greater than 1 cm thick) are recommended as an electrolyte reservoir with filter paper collection systems. The pad should be at least 1 cm larger than the electrode in all directions to prevent electrode-skin contact. It may be incorporated into sewn pockets designed to contain the electrode and prevent skin contact. The pads should be saturated by soaking in the electrolyte solution before application to the patient's skin.	Not Graded*	

Patient Information	Grade	References
• Hybrid systems (e.g. Wescor electrodes with aqueous electrolyte solutions, or Wescor gel discs used with non-Wescor electrodes) should not be used.	Not Graded*	
Iontophoresis - time, current • When aqueous electrolyte solutions are applied on pad supports to a current of 0.5 mA should be applied, and increased gradually to a maximum of 4 mA. Once 4 mA is attained the current should be maintained for a minimum of 3 minutes and a maximum of 5 minutes. Longer times should be necessary to increase sweat production, provided good electrical contact is maintained, by use of well maintained electrodes and suitably saturated pads.	B	(Instruction manual, 1979; Price & Spencer, 1977; Gibson & Cooke, 1959; Webster & Barlow, 1981; Webster, 1983; Kirk et al., 1983)
• When Wescor systems are used, the manufacturer's current and time recommendations should be followed. This will depend on the specific model used.	C	
• For both systems, the patient must be kept under close supervision throughout the iontophoresis period.	C	
Medium of Collection • During collection, sweat must be protected from contamination and evaporation (see example SOP in the original guideline document).	C	
• Sweat should be collected onto preweighed sodium chloride free filter paper or Wescor disposable collectors.	C	

Patient Information	Grade	References
• The size of the filter paper should be approximately equal to the area stimulated (i.e. the size of the electrolyte support pads).	C	
• Filter paper should be covered with a sheet of impervious material at least 1 cm larger in all dimensions than the filter paper.	C	
• The impervious material must be completely sealed to the skin surface using a suitable adhesive tape.	C	
• Filter paper and the inner side of the impervious material must never come into direct contact with the operator's hands.	C	
• Wescor collectors should be used according to the manufacturer's instructions, taking precautions to avoid direct contact of the sweat collecting surface with the operator's hands.	C	
Collection Time • Sweat should be collected for not more than 30 minutes and not less than 20 minutes.	B	(Reynolds, personal communication ; Price & Spencer, 1977; Shwachman & Mahmoodian, 1966; Webster & Quirante, 2000; Webster & Barlow, 1981; Kirk et al., 1983; Simmonds et al., 1989; Gibson & di Sant'Agnese, 1963; Schwarz, Simpson, & Ahuja, 1977; Hjelm, Brown, & Briddon, 1986)
• The Orion electrode should not be used.	B	(Price & Spencer, 1977; Denning et al., 1980)
Sweat Analysis Pre-analytical		

Patient Information	Grade	References
Storage before analysis • Throughout sweat collection (including transport and analysis) every effort should be made to minimise evaporation of the sample.	C	
• If storage is necessary before analysis, sweat collections on paper pads should be kept at 4 degrees Celsius for a maximum of 3 days and in appropriately sized, air tight containers which do not allow leakage or evaporation.	B	(Legrys, 1993)
• Liquid sweat from Macroduct collections can be stored in sealed macroduct tubing for up to 72 hours at 4 degrees Celsius. Haematocrit tubes sealed with plasticine are also suitable, providing an air gap is left between plasticine and sweat.	B	(Kirk, personal communication, 2001; Fahie-Wilson & Freedman, 1995)
• Sweat may be collected at remote sites and transported to the laboratory for analysis provided there is attention to storage details.	B	
Weighing		
• The same balance must be used throughout.	C	
• A balance sensitive to 0.0001 g must be used to weigh sweat.	C	
• Sweat collections onto paper pads should be weighed and analysed as soon as practicable.	C	
Definition of adequate sample • The sweat secretion rate measured as an average rate	B	(Price & Spencer, 1977; Webster & Quirante, 2000; Kirk et al., 1983; Simmonds et al., 1989;

Patient Information	Grade	References
over the collection period should not be less than 1 $g/m^2/min$. Collections below this rate should not be analysed. Insufficient sweat collections should not be pooled. The full sweat test should be repeated.		Hjelm, Brown, & Briddon, 1986; Gibson & de Sant'Agnese, 1963)
Analysis		
Elution of sweat from filter paper • When sweat is collected onto filter paper (refer to section 3.2.1 of the original guideline document) it should be eluted for a minimum of 40 minutes.	C	
Analytes • Sweat chloride concentration should be measured.	B	(Green, Dodds, & Pennock, 1985; Hall, Stableforth, & Green, 1990; Gleeson & Henry, 1991, Kirk et al., 1992)
• Sweat sodium must not be the only or primary analyte measured.	B	(Green, Dodds, & Pennock, 1985; Hall, Stableforth, & Green, 1990; Gleeson & Henry, 1991, Kirk et al., 1992)
• Sweat potassium measurement is not recommended.	B	(Shwachman, Mahmoodian, & Neff, 1981)
• Sweat conductivity measurement for the investigation of cystic fibrosis (CF) requires further study. If conductivity is measured, sweat chloride should also be measured until the relative merits of conductivity have been established.	B	(Heeley, Woolf, & Heeley, 2000; Mastella et al., 2000; Legrys, 2001; Heeley, Woolf, & Heeley, 2001; Webster, 2001)
• Sweat osmolality measurement is not recommended.	B	(Kirk, personal communication, 2001; Heeley, Woolf, & Heeley, 2000)
Methodology • Colorimetry, coulometry and	B	(Fahie-Wilson and Freedman, 1995; Finlay MacKenzie, 2001; Heeley,

Patient Information	Grade	References
ion selective electrodes (ISEs) are satisfactory methods for analysis of sweat chloride.		Woolf, & Heeley, 2000)
• Flame photometry or ion selective electrodes are satisfactory methods for analysis of sweat sodium.	B	(Finlay MacKenzie, 2001; Barbour, 1991; Northall & York, 1995)
• Conductivity measurement using the Wescor equipment is a satisfactory method of analysis.	B	(Finlay MacKenzie, 2001; Heeley, Woolf, & Heeley, 2000)
Report format The report format should include: i. Full patient identification ii. Date and time of test and date and time of report iii. Sweat weight/volume collected and minimum weight/volume acceptable for local sweat test parameters iv. Analytical results (mmol/L) It should be explicit on the report form which analyte(s) have been measured (i.e., chloride, sodium, conductivity [sodium chloride equivalent]). v. Reference ranges (see section 6 of the original guideline document) vi. Interpretation of the results (see section 6 of the original guideline document) vii. Recommendations for repeat testing if appropriate (see section 6.9 of the original guideline document)	C	
Quality		
• Sweat which has been subject to evaporation and/or contamination must not be	C	

Patient Information	Grade	References
measured.		
• The analytical range of the methods used must cover the concentration ranges found in normals and subjects with CF.	C	
• The analytical methods must be fully documented as SOP to comply with Clinical Pathology Accreditation (or equivalent standard). The SOP must include the analytical method(s), quality procedures, reporting, interpretation and safety aspects. An example SOP is provided (see Appendix Documents 2a and 2b of the original guideline document).	C	
• There must be an internal quality procedure (which differs from the calibration/standardisation procedure) at two concentrations (normal and intermediate or abnormal) for each analysis.	C	
• The analytical methods should each have a between batch coefficient of variation (CV) of 5% (or less) at a concentration of 40-50 mmol/L.	B	(Heeley, Woolf, & Heeley, 2000; Hall, Stableforth, & Green, 1990; Hammond, Turcios, & Gibson, 1994; Kirk et al, 1992; Ayers, 2000; Taylor & James, 1996)
• The laboratory must participate in a suitable external quality assessment scheme.	C	
• If chloride and sodium concentrations are widely discrepant, the test should be repeated.	B	
• Results which are not physiological should be questioned (i.e. chloride or	B	(Schulz, 1969)

Patient Information	Grade	References
sodium > 150 mmol/L).		
• For conductivity a provisional upper physiological limit of 170 mmol/L may be used pending further evidence.	C	
• Failed sweat collections (i.e. insufficient weight or volume) should not exceed 10% of the tested population (excluding repeats and tests carried out in sick/very young patients). There should be a target of 5%.	C	

• Performance of sweat testing should be reviewed on a regular basis. This should include:
  • Insufficient collections
  • as % of total tests
  • per operator
  • Analytical failure rate (i.e. % outside accepted quality control (QC) range)
  • External quality assessment performance
	C	

The laboratory should work with clinicians to audit sweat test results, in particular repeat collections, diagnoses and outcome of positive and intermediate results on a regular basis (see section 8 of the original guideline document).	C	
Interpretation of sweat electrolytes		
The following definitions are recommended for interpretation: • A sweat chloride concentration of >60 mmol/L supports the diagnosis of CF	B	(Green, Dodds, & Pennock, 1985; Hall, Stableforth, & Green, 1990; Rosenstein, 1999; Rosenstein & Cutting, 1998; Farrell & Koscik, 1996; "Correlation between genotype and phenotype," 1993; Davis et al., 1983; di Sant'Agnese et al., 1953)
• Intermediate chloride	B	(Green, Dodds, &

Patient Information	Grade	References
concentration of 40-60 mmol/L is suggestive but not diagnostic of CF.		Pennock, 1985; Hall, Stableforth, & Green, 1990; Rosenstein, 1999; Rosenstein & Cutting, 1998; Farrell & Koscik, 1996; Correlation between genotype and phenotype," 1993; Davis et al., 1983; di Sant'Agnese et al., 1953)
• A sweat chloride of less than 40 mmol/L is normal and there is a low probability of CF.	B	(Green, Dodds, & Pennock, 1985; Hall, Stableforth, & Green, 1990; Rosenstein, 1999; Rosenstein & Cutting, 1998; Farrell & Koscik, 1996; "Correlation between genotype and phenotype," 1993; Davis et al., 1983; di Sant'Agnese et al., 1953)
• Sodium should not be interpreted without a chloride result.	B	(Green, Dodds, & Pennock, 1985)
• Pending further data on conductivity measurements a value below 60 mmol/L (NaCl equivalents) is unlikely to be associated with CF. Values above 90 mmol/L support a diagnosis of CF.	B	(Hammonds, Turcios, & Gibson, 1994; Heeley, Woolf, & Heeley, 2000; Mastella et al., 2000).
• CF should not be diagnosed based on conductivity measurements alone.	B	(Hammonds, Turcios, & Gibson, 1994; Heeley, Woolf, & Heeley, 2000; Mastella et al., 2000).
Repeat Testing • A repeat sweat test is recommended when the sweat test result is not in keeping with the clinical phenotype and/or genotype.	C	
Further Investigations • Mutation analysis can be a useful diagnostic test, particularly in patients with a	B	(Augarten et al., 1995; Stern et al., 1978; Highsmith et al., 1994; Augarten et al., 1993; Strong et al., 1991;

Patient Information	Grade	References
mild or atypical phenotype where sweat chloride concentration may be intermediate.		Gilfillan et al., 1998)
• Nasal potential difference may be helpful as a confirmatory investigation for the diagnosis.	B	(Rosenstein, 1999; Alton et al., 1987; Delmarco et al., 1997)
• There is no routine place for the use of the mineralo-corticoid suppression adaptation of the sweat test.	B	(Hodson et al., 1983)
Responsibility for Testing and Training		

• Sweat collection must be performed by fully trained and experienced personnel:
  • Training schedules should be fully documented.
  • The procedure should be documented as an SOP.
  • Appropriate revalidation procedures should be in place.
	C	

• Sweat collection can be undertaken by a variety of health professionals.	C	
• Sweat analysis should be performed by qualified and experienced biomedical scientists or clinical scientists who are fully trained with regular validation: • Training and validation schedules should be fully documented.	C	
• A consultant (or equivalent) clinical chemist should have responsibility for training, assessment of competence and revalidation for all staff undertaking sweat tests.	C	

Patient Information	Grade	References
• A minimum number of 50 sweat tests per annum should be performed in any one centre.	C	
• A minimum of 10 collection procedures should be performed per person per annum.	C	
• The responsibilities for sweat testing, both collection and analytical, should rest with a consultant (or equivalent) clinical chemist and should be clearly understood by all operators and users; a mechanism for reporting any concerns about performance should be in place and clearly understood.	C	

* Grading of this recommendation changed following appraisal by the Royal College of Paediatrics and Child Health.

Definitions:

Levels of Evidence

The levels of evidence are based on the U.S. Agency for Health Care Policy (AHCPR) 1992

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II a: Evidence obtained from at least one well designed controlled study without randomisation

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IIb

- A planned scientific study with hypothesis
- A study not controlled
- An experimental study, with a low risk of bias

III

- Nonexperimental/observational study
- Investigation of a standard procedure

Grading of Recommendations

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B (levels II a, II b, III): Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of the recommendation

C (level IV): Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality

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CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

The sweat test, a quantitative measurement of electrolytes in sweat, remains vital in supporting the clinical diagnosis of cystic fibrosis (CF).

POTENTIAL HARMS

- There are published reports and personal communications which report clinical experience of the poor performance of sweat testing leading to an incorrect diagnosis. False negative results are of particular concern due to the potential for diagnostic delay. There is concern about the competency of the operator performing the collection, the need for quality control and external assessment to assess method performance, the competency of the analyst and interpretation. The causes of false positive and false negative results can arise from one or more of the following reasons: patients' physiology, inadequate sweat collection, poor/unreliable methodology, poor operator technique, misinterpretation.
- A theoretical risk of atrial fibrillation has never been documented.
- Burns or blisters are sporadically reported resulting from electrode-skin contact or inadequate reservoir of electrolyte solution between skin and electrode.
- Pilocarpine is toxic to eyes and skin.
- Sweat is considered to be a biohazard.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Guidelines for the performance of the sweat test for the investigation of cystic fibrosis in the UK. London: Royal College of Paediatrics and Child Health; 2003 Nov 1. 97 p. [123 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Nov

GUIDELINE DEVELOPER(S)

Association of Clinical Biochemists

GUIDELINE DEVELOPER COMMENT

The Multi-Disciplinary Working Group included representatives from the following organizations:

- UK National External Quality Assessment Schemes
- British Thoracic Society and Cystic Fibrosis Trust
- Royal College of Pathologists
- Royal College of Paediatrics & Child Health
- British Paediatric Respiratory Society

SOURCE(S) OF FUNDING

Association of Clinical Biochemists

Royal College of Pathologists

Royal College of Paediatrics and Child Health

GUIDELINE COMMITTEE

Guidelines Development Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Group Members: Dr. Anne Green (Chairman) Consultant Biochemist, Birmingham Children's Hospital NHSTrust; Professor Stuart Elborn, Consultant Physician, Belfast City Hospital, Belfast; Mr. Mike N. Fahie-Wilson, Principal Biochemist, Southend Hospital, Westcliff-on-Sea; Dr. Jean M. Kirk, Consultant Biochemist, Royal Hospital for Sick Children, Edinburgh, Lothian University Hospitals NHSTrust; Dr. Colin E. Wallis, Consultant Paediatrician, Great Ormond Street Hospital, London; Dr. Peter Weller, Consultant Paediatrician in Respiratory Medicine, Birmingham Children's Hospital NHS Trust

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

ENDORSER(S)

Royal College of Paediatrics and Child Health - Academic Institution

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Association of Clinical Biochemists Web site.

Print copies: Available from Dr. Anne Green, Consultant Paediatric Biochemist, Birmingham Children's Hospital, Steelhouse Lane, Birmingham, B4 6NH. Phone: (0121) 333 9922. Email: anne.green@bch.nhs.uk

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Sweat testing procedure. Staff training material. In: Guidelines for the performance of the sweat test for the investigation of cystic fibrosis in the UK. London: Royal College of Paediatrics and Child Health; 2003. p. 81-7.

Electronic copies: Available in Portable Document Format (PDF) from the Association of Clinical Biochemists Web site.

Print copies: Available from Dr. Anne Green, Consultant Paediatric Biochemist, Birmingham Children's Hospital, Steelhouse Lane, Birmingham, B4 6NH. Phone: (0121) 333 9922. Email: anne.green@bch.nhs.uk

PATIENT RESOURCES

The following is available:

- Example sweat test information sheet for patients/parents. In: Guidelines for the performance of the sweat test for the investigation of cystic fibrosis in the UK. London: Royal College of Paediatrics and Child Health; 2003. p. 79-80.

Electronic copies: Available in Portable Document Format (PDF) from the Association of Clinical Biochemists Web site.

Print copies: Available from Dr. Anne Green, Consultant Paediatric Biochemist, Birmingham Children's Hospital, Steelhouse Lane, Birmingham, B4 6NH. Phone: (0121) 333 9922. Email: anne.green@bch.nhs.uk

NGC STATUS

This summary was completed by ECRI on January 21, 2005. The information was verified by the guideline developer on February 11, 2005.

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Date Modified: 3/7/2005